CLAIMS

We claim:

1. A targeting construct comprising:

    (a) a first polynucleotide sequence homologous to at least a first portion of a TSH-R gene;

    (b) a second polynucleotide sequence homologous to at least a second portion of the TSH-R gene; and

    (c) a selectable marker.

2. A cell comprising a disruption in a TSH-R gene.
3. The cell of claim 2, wherein the cell is a murine cell.
4. The cell of claim 3, wherein the murine cell is an embryonic stem cell.
5. A non-human transgenic animal comprising a disruption in a TSH-R gene.
6. The non-human transgenic animal of claim 5, wherein the transgenic animal is a mouse.
7. A cell derived from the transgenic mouse of claim 6.
8. A method of identifying an agent that modulates the expression or function of a TSH-R gene, the method comprising:

    (a) providing a non-human transgenic animal comprising a disruption in the TSH-R gene;

    (b) administering the agent to the non-human transgenic animal; and

    (c) determining whether the expression or function of the disrupted TSH-R gene in the non-human transgenic animal is modulated.

9. A method of identifying an agent that modulates the expression or function of a TSH-R gene, the method comprising:

    (a) providing a cell comprising a disruption in the TSH-R gene;

    (b) contacting the cell with the agent; and

    (c) determining whether the expression or function of the TSH-R gene is modulated.

10. The method of claim 9, wherein the cell is derived from the non-human transgenic animal of claim 5.

11. An agent identified by the method of claim 8 or claim 9.
12. A transgenic mouse comprising a disruption in a TSH-R gene, wherein the transgenic mouse exhibits a thyroid abnormality, when compared to a wild-type mouse.
13. A transgenic mouse comprising a disruption in a TSH-R gene, wherein the transgenic mouse exhibits a growth disorder, when compared to a wild-type mouse.
14. A transgenic mouse comprising a disruption in a TSH-R gene, wherein the transgenic mouse exhibits, relative to a wild-type mouse, at least one of the following: a thymus abnormality; an abnormality of the subcutis; a reproductive abnormality; reduced organ weight; a reduced organ weight to body weight ratio; and a pituitary abnormality.
15. The transgenic mouse of claim 12, wherein the thyroid abnormality is reduced size, relative to a wild-type mouse.
16. The transgenic mouse of claim 12, wherein the thyroid abnormality is reduced follicle size.
17. The transgenic mouse of claim 13, wherein the growth disorder comprises one or more of reduced body size, reduced body weight and reduced body length.
18. The transgenic mouse of claim 14, wherein the thymus abnormality comprises one or more of reduced thymus weight, reduced thymus size and reduced thymus weight to body weight ratio.
19. The transgenic mouse of claim 14, wherein the thymus abnormality comprises hypoplasia.
20. The transgenic mouse of claim 14, wherein the abnormality of the subcutis comprises decreased fat.
21. The transgenic mouse of claim 14, wherein the reproductive abnormality is infertility.
22. The transgenic mouse of claim 14, wherein the mouse is male and the reproductive abnormality comprises a seminal vesicle abnormality.
23. The transgenic mouse of claim 22, wherein the seminal vesicle abnormality is reduced seminal vesicle size, relative to a wild-type mouse.
24. The male transgenic mouse of claim 22, wherein the seminal vesicle is substantially absent.

25. The transgenic mouse of claim 14, wherein the mouse is male and the reproductive abnormality comprises a testicular abnormality.
26. The male transgenic mouse of claim 25, wherein the testicles are immature.
27. The male transgenic mouse of claim 25, wherein the testicular abnormality comprises interstitial hypoplastic cells.
28. The transgenic mouse of claim 14, wherein the mouse is male and the reproductive abnormality comprises one or more of hypospermatogenesis and oligospermia.
29. The transgenic mouse of claim 14, wherein the reduced organ weight is associated with an organ selected from the group consisting of: spleen, liver, kidney, and heart.
30. The transgenic mouse of claim 14, wherein the reduced organ weight to body weight ratio is associated with an organ selected from the group consisting of: spleen, liver, kidney, and heart.
31. The transgenic mouse of claim 14, wherein the pituitary abnormality is in the adenohypophysis or pars distalis.
32. The transgenic mouse of claim 31, wherein where the pituitary abnormality is in the adenohypophysis, the adenohypophysis exhibits, relative to a wild-type mouse, at least one of: large cells; vacuolated cells; and reduced chromophils.
33. The transgenic mouse of claim 31, wherein where the pituitary abnormality is in the pars distalis, the pars distalis exhibits hypertrophy, relative to a wild-type mouse.
34. A transgenic mouse comprising a disruption in a TSH-R gene, wherein the transgenic mouse exhibits, relative to a wild-type mouse, a skeletal disorder selected from the group consisting of: small skeletal muscle; malformed femur; and dysplasia of the epiphyses of the femur, tibia and/or stifle joint.
35. A transgenic mouse comprising a disruption in a TSH-R gene, wherein the transgenic mouse exhibits, relative to a wild-type mouse, one or more of the following: reduced cellularity in bone marrow; immature kidneys; kidneys with lymphocytic infiltrates; lungs with lymphocytic infiltrates; and retinal fibrosis.
36. A transgenic mouse comprising a disruption in a TSH-R gene, wherein the transgenic mouse exhibits, relative to a wild-type mouse, a serum chemistry abnormality.
37. The transgenic mouse of claim 36, wherein the serum chemistry abnormality comprises an elevated blood urea nitrogen level.

38. A method of producing a transgenic mouse comprising a disruption in a TSH-R gene, the method comprising:

(a) introducing a TSH-R gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising the disruption in the TSH-R gene.

39. A cell derived from the transgenic mouse of claim 12, claim 13, or claim 14.

40. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a TSH-R gene, the method comprising:

(a) administering the agent to a transgenic mouse comprising a disruption in the TSH-R gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: a growth disorder; a thymus abnormality; a subcutis abnormality; a reproductive abnormality; reduced organ weight; reduced organ weight to body weight ratio; a thyroid abnormality; a pituitary abnormality; hunched posture; small head; short snout; abnormal snout; small eyes; small ears; abnormal activity level; hypoactivity; hyperactivity; abnormal metabolic rate; reduced responsiveness; non-responsiveness; small skeletal muscle; malformed femur; dysplasia of the epiphyses of the femur, tibia and/or stifle joint; histopathological lesions on organs; reduced cellularity in bone marrow; immature kidneys; kidneys with lymphocytic infiltrates; lungs with lymphocytic infiltrates; retinal fibrosis; and elevated blood urea nitrogen.

41. An agent identified by the method of claim 40.

42. An agonist or antagonist of a TSH receptor.